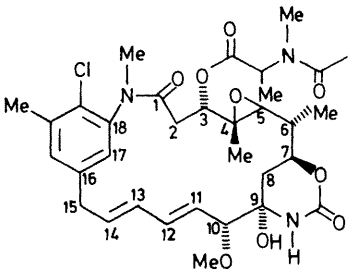
Studies Related to Maytansinoids

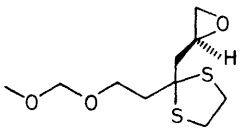
By DEREK H. R. BARTON,* STEPHEN D. GÉRO, and CHRISTOPHER D. MAYCOCK
(*Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France*)

Summary A rapid and high yielding route to optically active β-carbamoyloxy ketones of use in the synthesis of maytansinoids has been devised, starting from quinic acid.

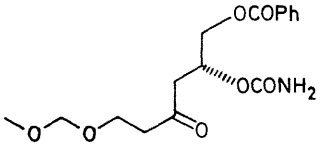
MAYTANSINE (**1**)[1] is a naturally occurring ansa macrolide of considerable clinical interest as an anticancer agent.[2] A number of research groups have made notable efforts towards its partial and total synthesis.[3]



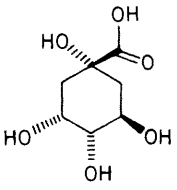
(1)



(2)

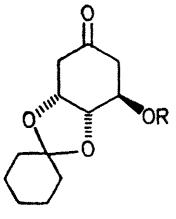


(3)

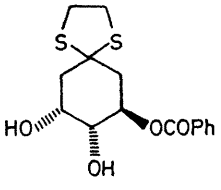


(4)

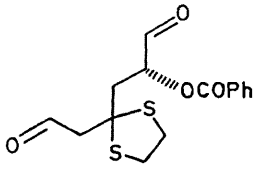
As part of a project aimed, ultimately, at the convergent synthesis of a modified maytansinoid and its congeners, in an enantiomerically pure form, we have prepared the epoxide (**2**), which is to become the C-6—C-11 portion of the macrocycle. We report also the preparation of the carbamate (**3**) which may retain some of the biological properties of maytansine. These, and other potentially usefully functionalised molecules, have been elaborated from D-(−)-quinic acid (**4**),[4] a relatively easily obtainable pseudo-carbohydrate.



(5) R = H
(6) R = COPh

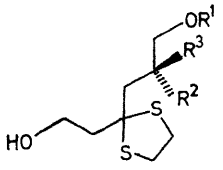


(7)

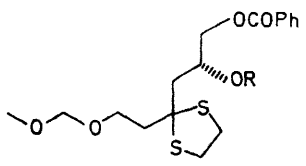


(8)

Treatment of the β-hydroxyketone (**5**)[4] with benzoyl chloride in pyridine afforded the monobenzoate (**6**) (90%), m.p. 120—121 °C, $[\alpha]_D$ + 68° (*c*, 1·45 in $CHCl_3$). Reaction of (**6**) with ethanedithiol and zinc iodide resulted in the diol (**7**) (80%), m.p. 115—116 °C, $[\alpha]_D$ ± 0° (*c*, 1·47 in $CHCl_3$); c.d. (EtOH) λ_{max} 223 nm ($\Delta\epsilon$ +1·75), by a simultaneous acetalisation of the carbonyl function and liberation of the *cis*-diol system. The diol (**7**) was then oxidised, using triphenylbismuth carbonate,[5] to the dialdehyde (**8**) which could not be isolated. It was, therefore, immediately reduced with sodium borohydride to give the expected product (**10**) (25%), $[\alpha]_D$ +23·2° (*c*, 15·6 in $CHCl_3$), along with (**9**) (50%), a liquid, $[\alpha]_D$ +3·7° (*c*, 0·96 in $CHCl_3$), the latter being the product resulting from benzoyl group migration. The secondary ester (**10**) could be converted into (**9**) (85%) using *NNN'N'*-tetramethylguanidine. The ester (**9**) was characterised as its bis-*p*-nitrobenzoate, m.p. 64—65 °C, $[\alpha]_D$ +9·5° (*c*, 1·48 in $CHCl_3$).



(9) R^1 = COPh, R^2 = OH, R^3 = H
(10) R^1 = H, R^2 = OCOPh, R^3 = H
(11) R^1 = COPh, R^2 = H, R^3 = OH

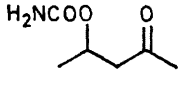


(12) R = H
(13) R = SO_2Me
(14) R = $CONH_2$

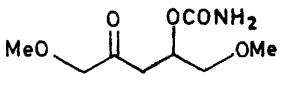
Selective protection of the free primary alcohol function of (**9**) was achieved using chloromethyl methyl ether to give the oily methoxymethyl ether (**12**) (55%), $[\alpha]_D$ −1·1° (*c*, 18·3 in $CHCl_3$), which was converted into its mesylate (**13**) (90%), $[\alpha]_D$ −19·9° (*c*, 5·5 in $CHCl_3$). Methanolysis of (**13**) (sodium methoxide in methanol) afforded the epoxide (**2**) (80%), $[\alpha]_D$ −1·6° (*c*, 0·76 in $CHCl_3$), as an oil.

Acylation of the secondary alcohol function of (**12**) with *p*-nitrophenyl chloroformate in pyridine, followed by ammonolysis (ammonia in Bu^tOH) furnished the carbamate (**14**) (80%). Regeneration of the ketone from the dithioacetal (**14**) with phenylseleninic anhydride[6] and propylene oxide gave (**3**), m.p. 71—72 °C. Surprisingly, (**3**) did not spontaneously cyclise as has been observed for model compounds of a similar type.[7] The acyclic structure of (**3**) was indicated by the resonance frequencies for the protons adjacent to the carbonyl group,[8] and by the occurrence of a signal at δ 204·7 p.p.m. in its ^{13}C n.m.r. spectrum. As a consequence, the model compounds (**15**) and (**16**) have been prepared in racemic form and also appear not to be cyclic.†

The absolute configuration at the asymmetric carbon atom in (**9**) is epimeric to that found at C-7 in the naturally occurring maytansinoids, hence a route to its enantiomer (**11**) was also developed from (**5**).



(15)

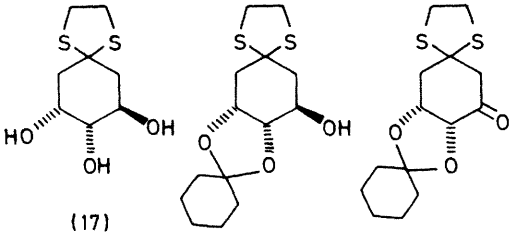


(16)

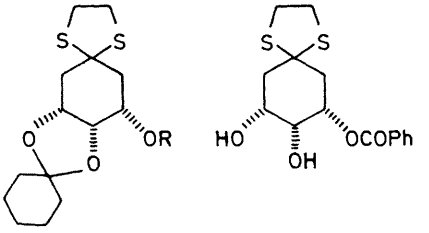
The latter was treated as before with ethanedithiol and zinc iodide giving the triol (**17**) (80%), m.p. 127—128 °C, $[\alpha]_D$ −35° (*c*, 1·25 in EtOH), which was reprotected as its

† Details of this will be published elsewhere.

cyclohexylidene derivative (**18**) (85%), m.p. 143—144 °C, $[\alpha]_D$ −45° (*c*, 1·76 in $CHCl_3$), by reaction with 1,1-dimethoxycyclohexane and sulphuric acid in dimethylformamide.



(17) (18) (19)



(20) R = H (22)
(21) R = COPh

Oxidation of the remaining hydroxy-group was effected (90%) with oxalyl chloride and dimethyl sulphoxide[9] and the product (**19**), m.p. 184—186 °C, $[\alpha]_D$ +15° (*c*, 1·03 in $CHCl_3$), reduced with lithium tri-t-butoxyaluminium hydride. The required alcohol (**20**), m.p. 121—122 °C, $[\alpha]_D$ +16° (*c*, 3·65 in $CHCl_3$), was obtained in 70% yield, whereas the alcohol (**18**) was only recovered in 6% yield. Acid-catalysed alcoholysis of the benzoate (**21**), m.p. 84—86 °C, $[\alpha]_D$ −24° (*c*, 1·33 in $CHCl_3$), rapidly produced the diol (**22**) (90%), m.p. 178—179 °C, $[\alpha]_D$ −27° (*c*, 1·7 in EtOH).

Triphenylbismuth carbonate oxidation followed by reduction, as before, furnished the diol (**11**) (50%) as an oil, $[\alpha]_D$ −3·9° (*c*, 1·1 in $CHCl_3$). This compound exhibited n.m.r. and i.r. spectra identical to those obtained for enantiomer (**9**).

We have demonstrated here the feasibility of preparing chiral compounds useful for the synthesis of simplified maytansinoids.

We thank Dr. P. Potier, Dr. and Mrs. Khuong-Huu and their collaborators for helpful discussions. C.D.M. thanks the Royal Society for a European Science Exchange Fellowship. Financial support from ATP-C.N.R.S. is gratefully acknowledged.

(*Received, 8th August* 1980; *Com.* 876.)

[1] S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F Bryan, *J. Am. Chem. Soc.*, 1972, **94**, 1354.
[2] P. N. Rao, E. J. Freireich, M. L. Smith, and Ti Li Loo, *Cancer Res.*, 1979, **39**, 3152.
[3] E. J. Corey, L. O. Weigel, D. Floyd, and M. G. Bock, *J. Am. Chem. Soc.*, 1978, **100**, 2916; A. I. Meyers, D. M. Roland, D. L. Comins, R. Henning, M. P. Fleming, and K. Shimizu, *ibid.*, 1979, **101**, 4732; E. J. Corey, L. O. Weigel, A. R. Chamberlin, and B. Lipshutz, *ibid.*, 1980, **102**, 1439; J. E. Foy and B. Ganem, *Tetrahedron Lett.*, 1977, 775; A. I. Meyers, D. L. Comins, D. M. Roland, R. Henning, and K. Shimizu, *J. Am. Chem. Soc.*, 1979, **101**, 7104; R. Bonjouklian and B. Ganem, *Tetrahedron Lett.*, 1977, 2835; M. Samson, P. De Clerq, H. De Wilde, and M. Vandewalle, *ibid.*, 1977, 3195; P. T. Ho, *Can. J. Chem.*, 1980, **58**, 858.
[4] J. Cleophax, S. D. Géro, J. Leboul, M. Akhtar, J. E. G. Barnett, and C. J. Pearce, *J. Am. Chem. Soc.*, 1976, **98**, 7110.
[5] D. H. R. Barton, D. J. Lester, W. B. Motherwell, and M. T. Barros Papoula, *J. Chem. Soc., Chem. Commun.*, 1979, 705.
[6] D. H. R. Barton, N. J. Cussans, and S. V. Ley, *J. Chem. Soc., Chem., Commun.*, 1978, 393 and references cited therein.
[7] E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 1975, 2643; A. I. Meyers and C. C. Shaw, *ibid.*, 1974, 717; A. I. Meyers and R. S. Brinkmeyer, *ibid.*, 1975, 1749; J. Lown, K. Majumdar, A. I. Meyers, and A. Hecht, *Bioorg. Chem.*, 1977, **6**, 453.
[8] M. Asai, E. Mizuta, M. Izawa, K. Haibara, and T. Kishi, *Tetrahedron*, 1979, **35**, 1079.
[9] A. J. Marcuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.